



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,133	07/11/2003	Ahmet Cuneyt Tas	MERCK-2704	1438

23599 7590 10/11/2005

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER

ROBERTS, LEZAH

ART UNIT	PAPER NUMBER
----------	--------------

1614

DATE MAILED: 10/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/617,133	Applicant(s) TAS, AHMET CUNEYT	
	Examiner Lezah W. Roberts	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-12 and 17-19 is/are rejected.
- 7) ☒ Claim(s) 3 and 13-16 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>25 Jan 2005</u> . | 6) <input type="checkbox"/> Other: ____. |

50

Art Unit: 1614

Detailed Action

Claims

Objections

Claim 3 objected to because of the following informalities: it recites ratio is 3 : 0.7 – 3 : -1. It should read 3 : 0.7 – 3 : 1. Appropriate correction is required.

Rejections, Obviousness

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1) Claims 1, 3-7, 9-12 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujishiro et al. in view of Chow et al.

Fujishiro et al. discloses the preparation and study of alpha-tricalcium phosphate/gelatin gel composite cements in order to increase the mechanical

Art Unit: 1614

strength of calcium phosphate cement. The reference teaches using self-setting cement, alpha-tricalcium phosphate (TCP) powder, and mixing it with 2.5-20 wt % of dried gelatin gel powder using an alumina mortar, as is recited in claim 1a (page 526, column 2). Using the wt % of the gelatin and that of the water disclosed by the reference, the amount of TCP powder is estimated to be at range from 62-30 wt %. The wt % ratio of the alpha TCP powder to the gelatin powder would range from 3: 0.2 – 3: 2, encompassing the mixing ratios recited in claims 3, 17 and 19. The cement pastes were prepared by kneading the TCP/gel mixture with deionized water and loading them into a stainless-steel mold. The molds were soaked in a moisture box under saturated water vapor pressure at 38 °C for 1 day. The samples were then soaked in tris-(hydroxymethyl)-aminomethane buffer solutions at pH 7.4 and 38 °C for 2-30 days (page 526, columns 1 and 2). Figure 1 (page 526) shows the samples being soaked in the buffer without the steel mold. It can be concluded the samples were taken out of the molds before being soaked in the buffer, as recited in claim 1d. After the cement products, with different amounts of gelatin gel, were soaked for 1 week in the buffer solution at 38 °C, pores were formed with diameters of 20 to 100 micrometers at 5 wt % of gelatin gel and 100 to 200 micrometers at 10-wt % of gelatin gel (page 527, column 2). Pore formation was due to leaching by soaking the composites in the buffer solution, which is recited in claims 1e, 11, and 17-19 where the temperature and the amount of time for leaching was 37 °C and a few days. Pore content increased with increasing gel content. Since the pore size seems to be dependent on the gel content, if the weight percent ranged from 10

Art Unit: 1614

% to 25 % it is probable the pore size would range from 100 – 500 micrometers as recited in claim 12. The method disclosed within the reference is similar to that of the first five steps recited in claim 1 with the exception of the solvents used for forming the paste and leaching out the gelatin. The difference in the temperature, 37 °C for the claims and 38 °C for the reference can be considered the same due to the error of a thermometer being +/- 2 °C. Claim 11 recites the time for leaching the sample was 2 days, this is also encompassed within the reference due to soaking of the samples ranged from 2-30 days. The reference differs from the claim insofar as to not disclose the use of water for the leaching out process; the use of Na₂HPO₄ to make the compositions; and treating the deposits thermally to burn out all remaining gel.

Chow et al. discloses methods and compositions relating to calcium phosphate cements, which self-harden substantially to hydroxyapatite (or hydroxylapatite (HA)) at ambient temperatures when in contact with an aqueous medium (see abstract). The cements disclosed in the invention are rapidly self-setting calcium phosphate cements, can set under ambient temperatures (room or body), and are less expensive than those available at time of disclosure. One of the criteria for claim 1, 5, and 19 and their dependent claims is the use of a self-setting calcium phosphate cement. The cement is made from dicalcium phosphate anhydrous (DCPA), dicalcium phosphate dehydrate (DCPD), amorphous calcium phosphate (ACP) or alpha or beta tricalcium phosphate (TCP) (column 7, lines 27-31), the compounds recited in claim 9. It is easy to use and readily modeled to accurately reconstruct bony cavities and missing bone

Art Unit: 1614

and to recreate contour defects of relatively non-stress bearing skeletal bone. HA formation in calcium phosphate slurries can be greatly accelerated by increased phosphate concentrations (column 5, line 60-63). An effective way to increase the phosphate concentration is by adding a non-calcium-containing salt of phosphoric acid such as Na_2HPO_4 (column 6, lines 26-29), step b of claim 1 and its dependent claims. The cement is stable and holds its molded shape in water (column 8, lines 4-22). The inventive cement may be supplied to the user in a variety of forms, including as powders or as a powder mixture, which is later mixed with the liquid diluent to make putty, as in the instant claims. It would be obvious to conclude the cement went through a grinding process in order to produce the powders. Various additives may be included in the inventive cements, slurries and pastes to adjust their properties and the properties of the hydroxyapatite products made from them. These include pore-forming agents. They can be in the form of granules, fibers, rods, sheets or grids (column 11, lines 51-65). The pore-forming agents create pores or channels sufficiently large to cause vascularization of tissue which infiltrates the cement once placed in the body. Such as the purpose of the gelatin powder recited in the instant claims. The agents are preferably substantially insoluble in the cement and can be removed by either resorption into body tissue, dissolution in physiological fluids, dissolution in solvents or heating after the cement has hardened (column 11, lines 66-67 and column 12, lines 1-6 and claims 32-33). The solvent can be water as in claim 1e and its dependent claims; claims 10; and 11. The temperature for burn out of the pore-forming agent is more than likely to be the

Art Unit: 1614

temperature, where it is known to decompose, as recited for claims 1, 5, their independent claims and claim 19, or the sintering temperature of the cement if it is higher than that of the temperature for decomposition of the composite, claims 4 and 7. The reference differs from the claims insofar as to not disclose the use of gelatin as the pore forming agent, specific solvents or conditions such as temperature for leaching the pore forming agents, or the sintering temperature for thermal treating to burn out the pore forming agents.

It would have been obvious to someone of ordinary skill in the art to have used the aqueous Na_2HPO_4 of the secondary reference in place of the deionized water in the primary reference, motivated by the desire to speed up the formation of the product in the primary reference and to make calcium phosphate granules that are easily made at ambient conditions as taught by the secondary reference. It would also have been obvious to someone of ordinary skill in the art to have thermally treated the samples to burn out the remaining gelatin of the primary reference motivated by the desire to obtain granules free from any type of pore forming material as taught by the secondary reference.

Regarding claims 4 and 7, the prior art does not disclose specific temperatures although it would have been obvious to have burned after leaching at a temperature, such as the sintering temperature of the calcium phosphate product motivated by the desire to maximize the removal of residual materials as would be expected by raising the temperature. This position is consistent with established precedent, which holds that normally, changes in result effective variables are not patentable where the difference involved is one of degree, not

Art Unit: 1614

of kind; experimentation to find workable conditions generally involves the application of no more than routine skill in the art. In re Aller 105 USPQ 233,235 (CCPA 1955).

2) Claims 2 and 8 rejected under 35 U.S.C. 103(a) as being unpatentable over Fujishiro et al. in view of Chow et al. further in view of Starling et al.

Fujishiro et al. and Chow et al. are discussed above and their combined disclosures differ from the instant claims insofar as to not disclose after squeezing the morsels from a device keeping them dry at room temperature for further machining as in claim 2 and grinding the calcium phosphate products after preparation as in claim 8.

Starling et al. discloses methods of making calcium phosphate microspheres and microcarriers. The microspheres are made from suitable mixtures of 0 to 100 % of HA and 0 to 100 % of TCP (column 4, lines 40-44) and can also be made from other calcium phosphates and mixtures thereof (column 10, lines 40-42). One of the mentioned microspheres made is a calcium phosphate hollow microsphere. The calcium phosphate is made into a slurry and mixed with wax or organic material. The mixture is sprayed under pressure through an orifice of sufficient size to allow passage of the organic microbeads with a coating of slurry. The beads are allowed to dry, as recited in claim 2. The organic microbead is removed by solvent extraction or a combination of solvent extraction and /or thermal decomposition. The microspheres are further dried and sintered (column 13 and 14). These microcarriers can be aggregated together

Art Unit: 1614

by adding them to a calcium phosphate powder slurry. The mixture is sintered and is sized by well known ceramic granulating/grinding and sieving methods (column 6, columns 48-62), as recited in claim 8. The reference differs from the instant claims insofar as to not disclose using self-setting cement; gelatin as the pore-former; using water as the solvent for dissolving microbeads; and Na_2HPO_4 as the solvent for mixing the calcium phosphate and pore-former.

It would have been obvious to one of ordinary skill in the art to have added the granulating/grinding and sieving method of the tertiary reference to the method suggested by the combined teachings of the primary and secondary references, motivated by the desire to produce porous granules of the appropriate size that can be used to make a slurry for implantation as bone filler, where the pores cause vascularization of tissue which infiltrates the cement, as disclosed by secondary reference. It would also have been obvious to have added the drying method of the tertiary reference to the method suggested by the combined teachings of the primary and secondary references, motivated by the desire to ensure stabilization of the product, if the desired shapes were already obtained, in order for it to withstand further treatment such as the sieving process as disclosed in the tertiary reference.

Claims 1-12 and 17-19 are rejected.

Allowable Subject Matter

Claims 13-16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art does not fairly suggest, teach or disclose the appropriate cooling conditions in order to obtain single-phase alpha or beta-TCP when preparing porous calcium phosphate products. It does disclose temperatures where one is stable over the other and the temperatures in which to obtain either TCP compounds, but does not specify the cooling to a certain temperature in a specific amount of time in order to get single-phase alpha or beta-TCP as recited by the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lezah W. Roberts whose telephone number is 571-272-1071. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1614

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Frederick Krass
Primary Examiner
Art Unit 1614



Lezah Roberts
Patent Examiner
Art Unit 1614

